REMARKS

Applicants wish to thank the Examiner for the consideration given to this case to date. Applicants have now had an opportunity to carefully consider the May 9, 2007 Office Action, and respectfully submit that the subject application is in condition for allowance based upon the amendments presented herein and the following remarks.

Status of Claims

The subject application was originally filed with 24 claims. On August 14, 2006, Applicants filed a First Preliminary Amendment, amending the subject application to add claims 25-33. On March 5, 2007, the Examiner issued a Restriction Requirement. On April 5, 2007, Applicants provisionally elected, with traverse in part, to prosecute claims 25-33. Applicants cancelled claims 15-24 without prejudice. Applicants traversed the restriction with respect to claims 1-14 and, in the May 9, 2007 Office Action, the Examiner rejoined claims 1-14. In this Response, Applicants cancel claims 5 and 12-24 without prejudice (rendering the Examiner's rejections of any of those claims moot), and amend claims 1, 6, 25, and 31. Accordingly, claims 1-4, 6-11, and 25-33 are pending in the subject application.

Summary of Office Action

In the May 9, 2007 Office Action, the Examiner:

(1) rejected claim 33 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement;

(2) rejected claim 31 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as their invention;

(3) rejected claims 1-10, 12-14, and 25-32 under 35 U.S.C. § 102(a) as being anticipated by Kao et al., Acad. Radiol. 2003, 10, 475-483 ("Kao");

(4) rejected claims 1, 3-7, 12-14, 25, 26, and 30 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,676,928 issued to Klaveness et al. ("Klaveness");

(5) rejected claims 1-4, 7-10, 12-14, 25, and 27-30 under 35 U.S.C. § 102(b) as being anticipated by Sachse et al., Invest. Radiol. 1997, 32, 44-50 ("Sachse");

(6) rejected claims 1, 3-8, 10, 14, 25, and 28-31 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 6,217,849B1 issued to Tournier et al. ("Tournier");

(7) rejected claims 1-4, 7-14, 25, and 27-30 under 35 U.S.C. § 103(a) as being unpatentable over Leike et al, Invest. Radiol. 2001, 36, 303-308 ("Leike") in view of Torchilin et al., Biochim. Biophys. Acta 1996, 1279, 75-83 ("Torchilin") or Sachse;

(8) rejected claims 1-14 and 25-32 under 35 U.S.C. § 103(a) as being unpatentable over Klaveness or Tournier or Kao in view of Torchilin;

(9) provisionally rejected claims 1-10 and 12-14 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 8-13, and 17 of co-pending Application No. 11/595,808; and

(10) provisionally rejected claims 25-33 under 35 U.S.C. § 101 as claiming the same invention as that of claims 27-35 of co-pending Application No. 11/568,936.

1. Rejection of claim 33 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Claim 33 is literally supported by the disclosure of the subject application as originally filed.

With respect to changing numerical range limitations, the Examiner's analysis must take into account which ranges one skilled in the art would consider inherently supported by the discussion in the original disclosure. M.P.E.P. § 2163.05(III). In In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976), the ranges described in the original specification included a range of "25%-60%" and specific examples of "36%" and "50%." A corresponding new claim limitation to "between 35% and 60%" met the description requirement. M.P.E.P. § 2163.05(III). In addition, in Union Oil of Cal. v. Atlantic Richfield Co., 208 F.3d 989, 997, 54 USPQ2d 1227, 1232-33 (Fed. Cir. 2000), the applicant described ranges of chemical properties which work in combination with ranges of other chemical properties to produce an automotive gasoline that reduces emissions. The description was found to provide an adequate written description even though the exact chemical components of each combination were not disclosed and the specification did not disclose any distinct embodiments corresponding to any claim at issue. Indeed, the Federal Circuit held that, "[T]he Patent Act and this court's case law recite only sufficient description to show one of skill in the . . . art that the inventor possessed the claimed invention at the time of filing." M.P.E.P. § 2163.05(III).

A person of ordinary skill in the art would recognize in the disclosure of the subject application as filed a description of the subject matter defined by claim 33.

First, claim 33 recites one first lipid or phospholipid, specifically hydrogenated soy phosphatidylcholine (HSPC), in an amount of about 58 to about 59 mole %. The subject application, as originally filed, discloses that an exemplary composition will comprise between about 60 and 75 mole % of one or more phospholipids with carbon chain lengths of 14-24

carbons. ¶ 0038. Example 1 and paragraph 0051 disclose the phospholipid in the amount of 55 mole %. ¶¶ 0051, 0069. Paragraph 0051 specifically discloses HSPC. ¶ 0051.

Second, claim 33 recites at least one second lipid or phospholipid which is derivatized with one or more polymers, specifically DSPE-MPEG2000, in an amount of about 5 to about 6 mole %. The subject application, as originally filed, discloses that an exemplary composition will comprise between about 1 and 20 mole % of the derivatized phospholipid. ¶ 0038. Example 1 and paragraph 0051 disclose the use of DSPE-MPEG2000 in the amount of 5 mole %.

Third, claim 33 recites at least one sterically bulky excipient, specifically cholesterol, which is present in the amount of about 36 to about 37 mole %. The subject application, as originally filed, discloses that an exemplary composition will comprise between about 25 and 40 mole % cholesterol. ¶ 0038. Likewise, Example 1 and paragraph 0051 disclose the use of cholesterol in an amount of 40 mole %.

Accordingly, a person of ordinary skill in the art would recognize in the disclosure of the subject application as filed a description of the subject matter defined by claim 33. In fact, the claim is literally supported by the specification. It is not necessary that the application describe the claim limitations exactly. See In re Wertheim, 541 F.2d at 262.

As such, Applicants respectfully request that the Examiner withdraw the rejection of claim 33 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

2. Rejection of claim 31 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as their invention.

Applicants have amended claim 31. Claim 31, as amended, particularly points out and distinctly claims the subject matter which Applicants regard as their invention. Applicants

respectfully request that the Examiner withdraw the rejection of claim 31 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as their invention.

3. Rejection of claims 1-10, 12-14, and 25-32 under 35 U.S.C. § 102(a) as being anticipated by Kao.

Kao does not constitute prior art under 35 U.S.C. § 102(a) because the article is describing Applicants' own work.

M.P.E.P. § 715.01(c)(I) provides in part:

> Where the applicant is one of the co-authors of a publication cited against his or her application, . . . the applicant may overcome the rejection by filing a specific affidavit or declaration under 37 CFR 1.132 establishing that the article is describing applicant's own work.

M.P.E.P. § 715.01(c)(I). M.P.E.P. § 716.10 similarly provides:

> [I]t is incumbent upon the inventors named in the application . . . to rebut a rejection under 35 U.S.C. 102(a) or (e), to provide a satisfactory showing by way of affidavit under 37 CFR 1.132 that the inventorship of the application is correct in that the reference discloses subject matter derived from the applicant rather than invented by the author, patentee, or applicant of the published application notwithstanding the authorship of the article or the inventorship of the patent or published application. In re Katz, 687 F.2d 450, 455, 215 USPQ 14, 18 (CCPA 1982) (inquiry is appropriate to clarify any ambiguity created by an article regarding inventorship and it is then incumbent upon the applicant to provide "a satisfactory showing that would lead to a reasonable conclusion that [applicant] is the ... inventor" of the subject matter disclosed in the article and claimed in the application).
>
> An uncontradicted "unequivocal statement" from the applicant regarding the subject matter disclosed in an article, patent, or published application will be accepted as establishing inventorship. In re DeBaun, 687 F.2d 459, 463, 214 USPQ 933, 936 (CCPA 1982).

M.P.E.P. § 716.10.

Applicants attach hereto as **EXHIBIT A** a 1.132 declaration by Applicants stating, unequivocally, that the cited disclosure in Kao was conceived and invented by Applicants, rather than invented by the author of the publication, notwithstanding the authorship of the publication. In addition, Applicants attach hereto as **EXHIBIT B** a 1.132 declaration by Kenneth C. Beck—the only author on Kao not listed as an inventor in the subject application—stating, unequivocally, that he is not an inventor with respect to any of the claims of the subject application, notwithstanding the authorship of the publication.

In light of the above, Applicants respectfully request that the Examiner withdraw the rejection of claims 1-4, 6-10, and 25-32 under 35 U.S.C. § 102(a) as being anticipated by Kao.

4. Rejection of claims 1, 3-7, 12-14, 25, 26, and 30 under 35 U.S.C. § 102(b) as being anticipated by Klaveness.

Under 35 U.S.C. § 102, a claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Klaveness fails to expressly or inherently disclose each and every limitation recited in amended claims 1 and 25.

With respect to amended claim 1, Klaveness does not disclose a pharmaceutically acceptable excipient capable of stabilizing the sterically stabilized liposomes in blood. Instead, Klaveness discloses that, "a stabilizing agent such as $EDTANa_2Ca$ and TRIS buffer can be added." Office Action, at p. 5. However, the pharmaceutically acceptable excipient of claim 1 (e.g., cholesterol) stabilizes the sterically stabilized liposome itself in the blood because it is within the bilayer. In contrast, $EDTANa_2Ca$ and TRIS buffer stabilize the composition for, e.g., storage. $EDTANa_2Ca$ and TRIS buffer do not partition into the bilayer of the liposome; instead, they remain completely in the external phase. Upon injection, the $EDTANa_2Ca$ and TRIS buffer solution is immediately diluted away by the blood.

Similarly, with respect to amended claim 25, Klaveness does not disclose a sterically bulky excipient capable of stabilizing the sterically stabilized liposome in blood. The Examiner

notes, "In regards to stabilizing the liposomal composition, a stabilizing agent such as EDTANa2Ca and TRIS buffer can be added." Office Action, at p. 5. Applicants respectfully disagree with the Examiner's characterization of $EDTANa_2Ca$ and TRIS buffer on two grounds. First, $EDTANa_2Ca$ and TRIS buffer are not sterically bulky; they are relatively small molecules. Second, as noted above, the sterically bulky excipient of amended claim 25 (e.g., cholesterol) actually stabilizes the sterically stabilized liposome itself in the blood because it is within the bilayer. As stated above, $EDTANa_2Ca$ and TRIS buffer do not partition into the bilayer of the liposome; instead, they remain completely in the external phase. As noted in Klaveness, "This type of buffer has a lower pH at autoclaving temperatures, which increases the stability of the X-ray contrast agent during autoclaving. . . . TRIS surprisingly also provides improved shelf life." Klaveness, col. 8, lines 15-20. Again, upon injection, the $EDTANa_2Ca$ and TRIS buffer solution is immediately diluted away by the blood.

In sum, Klaveness' recitation of $EDTANa_2Ca$ and TRIS buffer has no relevance to the pharmaceutically acceptable excipient capable of stabilizing the sterically stabilized liposomes in blood recited in amended claim 1, or the sterically bulky excipient capable of stabilizing the sterically stabilized liposome in blood recited in amended claim 25. As such, Klaveness fails to expressly or inherently disclose each and every limitation recited in amended claims 1 and 25. Claims 3, 4, 6, 7, 9, and 10 depend, either directly or indirectly, from amended claim 1. Claims 26 and 30 depend directly or indirectly from amended claim 25. Dependent claims are construed to include all of the limitations of the "parent" claim. These limitations are considered to be incorporated by reference into the dependent claim. 35 U.S.C. § 112, ¶ 4. Thus, Klaveness necessarily fails to disclose each and every limitation of claims 3, 4, 6, 7, 9, 10, 26, and 30 as well.

With further regard to claim 30, Applicants respectfully disagree with the Examiner's characterization of Klaveness as not requiring autoclaving. Indeed, Klaveness appears to be wholly premised upon an autoclaving step. Klaveness, col. 3, line 64 through col. 4, line 7. Every preparation Example recited in Klaveness includes the autoclaving step and the claims

themselves explicitly refer to the invention as "[a]n autoclaved diagnostic composition . . . ." Klaveness, at claim 1.

As such, Applicants respectfully request that the Examiner withdraw the rejection of claims 1, 3, 4, 6, 7, 9, 10, 25, 26, and 30 under 35 U.S.C. § 102(b) as being anticipated by Klaveness.

5. Rejection of claims 1-4, 7-10, 12-14, 25, and 27-30 under 35 U.S.C. § 102(b) as being anticipated by Sachse.

Sachse fails to disclose, either expressly or inherently, each and every limitation of amended claims 1 and 25.

With respect to amended claim 1, Sachse fails to disclose a sterically stabilized liposome containing a phospholipid which is derivatized with a polymer chain, the sterically stabilized liposome being less than about 150 nanometers in average diameter. Amended claim 25 likewise recites an average diameter size of less than about 150 nm. In contrast, Sachse discloses that inclusion of DSPE-PEG results in a vesicle size of 204 nm. (Sachse, p. 3).

As such, Sachse fails to disclose, either expressly or inherently, each and every limitation of amended claims 1 and 25. Claims 2-4 and 7-10 depend directly or indirectly from amended claim 1. Claims 27-30 depend directly or indirectly from amended claim 25. Thus, Sachse necessarily fails to disclose each and every claim limitation of claims 2-4, 7-10, and 27-30.

For the foregoing reasons, Applicants respectfully request that the Examiner withdraw the rejection of claims 1-4, 7-10, 25, and 27-30 under 35 U.S.C. § 102(b) as being anticipated by Sachse.

6. Rejection of claims 1, 3-8, 10, 14, 25, and 28-31 under 35 U.S.C. § 102(b) as being anticipated by Tournier.

Tournier fails to disclose, either expressly or inherently, each and every limitation of amended claims 1 and 25.

Amended claims 1 and 25 each recite that the sterically stabilized liposomes have an average diameter of less than about 150 nm. With respect to this limitation, the Examiner states that, "The injected dose of the liposomal contrast agent is 50-100 mg I/kg and the size of the vesicle may be 100 nm (column 7, lines 36-44)." Office Action, at p. 6. However, column 7, lines 36-47 actually provide as follows:

> Now, as generally admitted in the imaging field, sufficient imaging contrast in the blood-pool advantageously requires an injected dose of at least about 50-100 mg of iodine/kg of body weight and for the safety reasons, this is distributed in an amount of injectable liquid preferably not exceeding 1 ml/kg. Hence, ***if*** we wish to distribute (by means of a liposome suspension) 100 mg of iodine in 1 ml of injectable liquid, i.e. to have a concentration (C_{IS}) of iodine in the liposome suspension of 100 mg/ml using 100 nm vesicles, we ***should*** use a liposome suspension of concentration (C_{Lip})=100/0.52=190 mg of lipids/ml.

Tournier, col. 7, lines 36-46 (emphasis added). It is clear from this paragraph that Tournier did not make, use, or even desire to make and use 100 nm vesicles. This paragraph is no more than a theoretical calculation to demonstrate the impracticability of using such a small vesicle size. Rather, Tournier teaches vesicles in the 200 nm to 1 μm range, with an average diameter of 400 nm. Tournier, col. 4, lines 60-67. Applicants respectfully submit that Tournier's use of a round number (100 nm) in a normative calculation may not fairly be said to mean that "the vesicle may be 100 nm." Moreover, no indication exists that Tournier even contemplated a sterically stabilized liposome having such a tiny vesicle size. In stark contrast, amended claims 1 and 25 each recite a sterically stabilized liposome having an average diameter of less than about 150 nm.

As such, Tournier fails to disclose, either expressly or inherently, each and every limitation of amended claims 1 and 25. Claims 3, 4, 6-8, and 10 depend directly or indirectly

from amended claim 1. Claims 28-31 depend directly or indirectly from amended claim 25. Thus, Tournier fails to disclose each and every limitation of claims 3, 4, 6-8, 10, and 28-31 as well.

For the foregoing reasons, Applicants respectfully request that the Examiner withdraw the rejection of claims 1, 3, 4, 6-8, 10, 25, and 28-31 under 35 U.S.C. § 102(b) as being anticipated by Tournier.

7. **Rejection of claims 1-4, 7-14, 25, and 27-30 under 35 U.S.C. § 103(a) as being unpatentable over Leike in view of Torchilin or Sachse.**

The factual inquiries relevant to establishing obviousness under 35 U.S.C. § 103(a) are set forth in Graham v. John Deere Co., 383 U.S. 1 (1966):

a. Determining the scope and contents of the art being cited.

b. Ascertaining the differences between the prior art and the claims at issue.

c. Resolving the level of ordinary skill in the pertinent art.

d. Considering objective evidence present in the application indicating obviousness or nonobviousness.

In its May 3, 2007 Memorandum, the Office offered the following additional guidance relating to the proper obviousness analysis:

> [I]n formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.

(May 3, 2007 PTO Memorandum, p. 2).

In addition, to establish prima facie obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art. M.P.E.P. § 2143.03.

a. The scope and contents of Leike, Torchilin, and Sachse.

Leike is directed to iopromide contrast (i.e., non-radioactive) carrying liposomes that are potentially useful as CT blood-pool agents. As noted by the Examiner, Leike does not teach phospholipids derivatized with polymer chains. Leike, pp. 303 ("Iopromide liposomes composed of SPC, cholesterol, and SPG in a molar ratio of 6:3:1 were prepared . . . .") and 305. In fact, Leike specifically states, "In the present study, tolerance, elimination, and diagnostic properties of ***unmodified (conventional)*** iopromide-carrying blood-pool liposomes were studied." Leike, p. 306 (emphasis added). The Examiner also correctly implies that Leike does not teach liposomes having an average diameter of less than 150 nm. Leike, pp. 305 ("The resulting mean diameter amount to 201 nm . . . .") and 307 ("mean diameter ≈ 200 nm"). Finally, Leike does not teach the removal of unencapsulated contrast agent. Leike, p. 305 ("The iopromide-carrying liposomes . . . were used without prior removal of the unencapsulated contrast agent.").

Torchilin's relevance to the subject application is not evident to Applicants. Torchilin addresses biodistribution of liposomes in acutely damaged tissues with broken-down vascular and cell membrane barriers. This is why the size of the liposomes in Torchilin is relatively insignificant. Indeed, the primary goal of the Torchilin study was to characterize immunoliposomes, specifically those that have antibodies to myosin on their exterior. Torchilin, Abstact and p. 76. In addition, Torchilin teaches radioactively labeled liposomes. In other words, Torchilin does not teach the use of non-radioactive contrast enhancing agents.

Sachse is directed to iopromide-carrying liposomes (SPC/CH/SPG 6:3:1). Sachse does not teach liposomes having polymer-chain derivatized phospholipids wherein the liposomes have an average diameter of less than about 150 nm. Sachse, p. 3, para. 8. In fact, Sachse warns that the inclusion of SDPE-PEG leads to a "drastic increase in vesicle size." Id. Sachse also does not teach the removal of unencapsulated contrast agent. ("Iopromide-carrying liposomes . . . [were] used without prior removal of the unencapsulated contrast agent."). Id.

b. The differences between the cited art and the claims at issue

Claim 1, as amended, recites sterically stabilized liposomes containing or associated with one or more nonradioactive contrast-enhancing agents, wherein the sterically stabilized liposomes comprise a pharmaceutically acceptable excipient capable of stabilizing the sterically stabilized liposomes in blood, and wherein the sterically stabilized liposomes contain a phospholipid which is derivatized with a polymer chain, the sterically stabilized liposome being less than about 150 nanometers in average diameter.

Amended claim 25 recites, among other things: (1) at least one second lipid or phospholipid which is derivatized with one or more polymers; (2) the at least one sterically stabilized liposome is less than about 150 nanometers in average diameter; and (3) the at least one sterically stabilized liposome is associated with at least one nonradioactive contrast enhancing agent.

The primary reference cited by the Examiner, Leike, does not even teach sterically stabilized liposomes. Specifically, Leike does not teach polymer-derivatized phospholipids as claimed. In fact, Leike specifically and explicitly avoids the use of such modified phospholipids. Leike also does not teach liposomes (sterically stabilized or otherwise) having an average diameter of less than 150 nm as claimed. Rather, the unmodified liposomes disclosed in Leike have a mean diameter of 201 nm. Clearly, Leike addresses a fundamentally different inventive concept than what is recited in amended claim 1 and claim 25.

Applicants respectfully submit that neither Torchilin nor Sachse supply the missing teachings to render amended claims 1 and 25 obvious.

First, as noted above, Leike teaches the use of non-radioactive contrast enhancing agents and explicitly teaches away from the use of modified phospholipids. Torchilin, in stark contrast, teaches biodistribution of liposomes in acutely damaged tissues with broken-down vascular and cell membrane barriers using radioactively labeled liposomes (rendering Torchilin inapposite to the subject application ab initio) that do contain PEGylated phospholipids. Thus, no motivation

exists to combine Leike and Torchilin. See May 3, 2007 PTO Memorandum, at p. 2 ("it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed"). Moreover, Torchilin's radioactively labeled, derivatized liposomes may very well render Leike's compositions inoperable. It is well-settled that if a proposal for modifying the prior art in an effort to attain the claimed invention causes the art to become inoperable or destroys its intended function, then the requisite motivation to make the modification would not have existed. See In re Fritch, 972 F.2d 1260, 1265 n.12 ("A proposed modification [is] inappropriate for an obviousness inquiry when the modification render[s] the prior art reference inoperable for its intended purpose.").

Second, even if a person of ordinary skill in the art would read Leike and combine it with Sachse (notwithstanding the clear avoidance of modified phospholipids in Leike, and the clear emphasis on using such modified phospholipids in Sachse), the combination of the two references still would not teach or suggest every limitation of either amended claim 1 or amended claim 25. Specifically, both references explicitly teach liposomes having a mean diameter in excess of 200 nm and, thus, fail to meet the limitation in amended claims 1 and 25 that the sterically stabilized liposomes have an average diameter of less than about 150 nm.

Based on the foregoing, Applicants respectfully request that the Examiner withdraw the rejection of amended claim 1 and its directly or indirectly dependent claims 2-4 and 7-11, and amended claim 25 and its directly or indirectly dependent claims 27-30 under 35 U.S.C. § 103(a) as being unpatentable over Leike in view of Torchilin or Sachse.

8. Rejection of claims 1-14 and 25-32 under 35 U.S.C. § 103(a) as being unpatentable over Klaveness or Tournier or Kao in view of Torchilin.

As noted above, Kao does not constitute prior art vis-à-vis the subject application. As such, Applicants will focus their analysis on the remaining cited references, Klaveness, Tournier, and Torchilin.

a. The scope and contents of Klaveness, Tournier, and Torchilin.

Klaveness does not disclose a pharmaceutically acceptable excipient capable of stabilizing sterically stabilized liposomes in blood. Klaveness also fails to disclose a sterically bulky excipient capable of stabilizing the sterically stabilized liposome. Moreover, the Klaveness reference is undeniably based upon an autoclaving step. *See* Klaveness, col. 3, line 64 through col. 4, line 7. Every preparation Example recited in Klaveness includes the autoclaving step and the claims themselves explicitly refer to the invention as "[a]n autoclaved diagnostic composition . . . ." Klaveness also does not provide a single instance of the use of a polymer-derivatized lipid or phospholipid. Klaveness merely makes passing (and, arguably, non-enabling) reference that, "compositions of the invention, for use in any type of imaging, may if desired be modified with materials such as polyethyleneglycol to increase the circulation half-life of the liposomes." Klaveness, col. 11, lines 7-10. Klaveness does, however, teach the use of non-radioactive contrast enhancing agents. Klaveness, col. 1, lines 23-39.

Tournier teaches vesicles in the 200 nm to 1 μm range, with an average diameter of 400 nm. Tournier, col. 4, lines 60-67. Tournier does not make, use, or even desire to make or use vesicles having an average diameter of less than about 150 nm as claimed in amended claims 1 and 25. Indeed, Tournier explicitly and clearly teaches away from the use of such "tiny" liposomes:

> The use of tiny liposome vesicles of the kind proposed in EP-A-0 442 962 for the delivery of drugs (in the order of 50 nm or less) ***are*** [sic] ***therefore unpractical*** for blood-pool imaging. Much the same applies to the proposals of Gabison et al. in Biochim. Et Biophys. Acta 1103 (1992) 94-100 and I.A.J.M. Bakker-Woudenberg et al. ibid 318-326 directed to liposomes with an average size between 0.07 μm and 0.1 μm and prolonged residence times in the blood.

Tournier, col. 3, lines 14-22 (emphasis added). Indeed, as explicitly noted by Tournier, at col. 5, line 66-col. 6, line 7:

> It is advantageous to use suspensions in which the vesicles have a size distribution as narrow as possible around a nominal value selected in the give 0.2 to 1.0 μm range and preferably in the range between 0.2 and 0.6 μm. For instance, if the selection desirably involves a suspension of vesicles of, say 0.4 μm, it is preferably that at least 80%, according to volume distribution, of the vesicle [sic] have a size of 0.4 μm±10%. The narrow width of the vesicle size distribution band can be considered here as a quality factor.

Tournier, col. 5, line 66-col. 6, line 7.

In addition, and, perhaps, more importantly, Tournier clearly disavows and teaches away from the use of polymer-derivatized phospholipids. See, e.g., col. 3, lines 30-35:

> ***[T]he production of liposomes with the "stealth factors" is rather cumborsome. In addition***, "stealth factored" liposomes are known to have very low entrapment capacity and while such liposomes may be suitable to carry specific drugs, and therefore useful in therapy, ***they are almost useless in imaging***.

Tournier, col. 3, lines 30-35 (emphasis added). See also, col. 3, lines 64-67:

> The blood pool agents contain liposomes with astounding so called "stealth" properties without requiring incorporation of the priorly recognized "stealth factors".

Tournier, col. 3, lines 64-67. See also, col. 5, lines 50-62:

> It is also noteworthy that the additional incorporation of the priorly recognised "stealth factors" into the liposomes and the suspensions of the invention (which are useful in other liposome formulations) will bring no further improvement in the "stealth" properties of the present suspensions. The incorporation of these factors into the liposomes will thus have insufficient impact on the residence time of the liposomes of the invention in the blood. Actually, ***the incorporation of recognized stealth factors to the formulations of the present liposomes suspensions may even be detrimental*** as the captured volume E_c (entrapped volume/weight of lipid) may be significantly reduced.

Tournier, col. 5, lines 50-62 (emphasis added).

Torchilin, as described above, is irrelevant to the subject application. Torchilin addresses biodistribution of liposomes in acutely damaged tissues with broken-down vascular and cell membrane barriers. This is why the size of the liposomes in Torchilin is relatively insignificant.

Torchilin, Abstact and p. 76. In addition, Torchilin teaches radioactively labeled liposomes. In other words, Torchilin does not teach the use of non-radioactive contrast enhancing agents.

b The differences between the cited art and the claims at issue.

Claim 1, as amended, recites sterically stabilized liposomes containing or associated with one or more nonradioactive contrast-enhancing agents, wherein the sterically stabilized liposomes comprise a pharmaceutically acceptable excipient capable of stabilizing the sterically stabilized liposomes in blood, and wherein the sterically stabilized liposomes contain a phospholipid which is derivatized with a polymer chain, the sterically stabilized liposomes being less than about 150 nanometers in average diameter.

Amended claim 25 recites, among other things: (1) at least one second lipid or phospholipid which is derivatized with one or more polymers; (2) the at least one sterically stabilized liposome is less than about 150 nanometers in average diameter; and (3) the at least one sterically stabilized liposome is associated with at least one nonradioactive contrast enhancing agent.

The first primary reference cited by the Examiner, Klaveness, does not disclose a pharmaceutically acceptable excipient capable of stabilizing the sterically stabilized liposome in blood (as recited in amended claim 1). Klaveness also fails to disclose a sterically bulky excipient capable of stabilizing the sterically stabilized liposome in blood (as recited in amended claim 25). Moreover, the Klaveness invention is undeniably based upon an autoclaving step.

Applicants respectfully submit that no motivation exists to combine Klaveness with Torchilin to render amended claim 1 and/or amended claim 25 obvious. A person of ordinary skill in the art would not read Klaveness, a reference teaching the use of non-radioactive contrast enhancing agents in autoclaved liposomes, and combine it with Torchilin, a reference teaching biodistribution of liposomes in acutely damaged tissues with broken-down vascular and cell membrane barriers using radioactively labeled liposomes, where autoclaving is not contemplated. PTO Memorandum, at p. 3.

Given Tournier's clear disavowal of "tiny" liposomes and the use of "stealth" factors (as described exhaustively above), Applicants respectfully submit that under no circumstances would a person of ordinary skill in the art be motivated to combine the second primary reference, Tournier, with any reference to arrive at the content of the subject application. Surely, Torchilin's use of liposomes of 120-150 nm would be "unpractical" in view of Tournier. Likewise, Torchilin's use of PEGylated phospholipids would be "detrimental" to the invention described in Tournier. See In re Fritch, 972 F.2d at 1265 n.12.

Based on the foregoing, Applicants respectfully request that the Examiner withdraw the rejection of amended claim 1 and its directly or indirectly dependent claims 2-4 and 5-11, and amended claim 25 and its directly or indirectly dependent claims 26-32 under 35 U.S.C. § 103(a) as being unpatentable over Klaveness or Tournier or Kao in view of Torchilin.

9. Provisional rejection of claims 1-10 and 12-14 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 8-13, and 17 of co-pending Application No. 11/595,808.

On August 9, 2007, Applicants filed a preliminary amendment cancelling claims 1-3, 8-13, and 17 from co-pending Application No. 11/595,808. As such, the Examiner's rejections based upon that reference are moot. Applicants respectfully request that the Examiner withdraw the provisional rejection of claims 1-10 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 8-13, and 17 of co-pending Application No. 11/595,808.

10. Provisional rejection of claims 25-33 under 35 U.S.C. § 101 as claiming the same invention as that of claims 27-35 of co-pending Application No. 11/568,936.

On August 9, 2007, Applicants filed a preliminary amendment cancelling claims 27-35 of co-pending Application No. 11/568,936. As such, the Examiner's rejections based upon that reference are moot. Applicants respectfully request that the Examiner withdraw the provisional rejection of claims 25-33 under 35 U.S.C. § 101 as claiming the same invention as that of claims 27-35 of co-pending Application No. 11/568,936.

CONCLUSION

In view of the remarks above and the amendments presented herein, it is believed that claims 1-4, 6-11, and 25-33, as amended, are in condition for allowance and notice to such effect is respectfully requested. If the Examiner thinks a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at the phone number provided below.

If additional fees are due in connection with this Amendment, the Commissioner is authorized to charge Deposit Account No. 02-2051, identifying Docket No. 27428-4.

Respectfully submitted,

Dated: August 9, 2007

By: /s/Benjamen E. Kern
Benjamen E. Kern
Reg. No. 56,391

BENESCH, FRIEDLANDER,
COPLAN & ARONOFF, LLP
88 E. Broad Street, Suite 900
Columbus, Ohio 43215-3506
(614) 223-9300